

fraction containing one or more components that reduce an excessive Th1 immune response.

Amendments to the claims are indicated in the attached "Marked Up Version of Amendments" (page i).

REMARKS

Claims 24, 26 and 28-32 are currently pending in the application. Claim 26 is amended. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added, nor are new grounds raised for further search or consideration.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 24, 26 and 28-32 are rejected on the grounds that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims. The Office Action asserts that the specification does not reasonably provide enablement for a method of screening an helminthic parasite preparation for one or more components that reduce excessive Th1 immune responses, where the preparation is prepared by fractionating and sub-fractionating the helminthic preparation.

The Office Action asserts (at pages 4-5) that the specification (1) provides no guidance with regard to how one would obtain subfractions of the homogenate, (2) provides no guidance with regard to which sub-fractions would possess the claimed functions, (3) provides no guidance with regard to how the sub-fractions were obtained and used in the assay, (4) provides no showing of fractionation or a sub-fractionation of helminthic preparations, (5) is silent on how one would perform the "assay" step *in vivo*, (6) provides no guidance on what parameters or markers are measured, how the parameters or marker are measured, or how samples are obtained. Each of these issues is addressed below.

How to Obtain Subfractions of the Homogenate

Homogenization is discussed in the specification at page 18, line 25 to page 19, line 11. "Fractionating" is defined in the specification, at page 9, lines 17-19, as "the process of dividing a helminthic homogenate or fraction of a homogenate into smaller sub-portions or fractions on the basis of some physical, chemical or biochemical property." Sub-fractionating is also discussed (at page 8, lines 19-23) as subjecting a fraction to a further step of fractionating. The specification also states (at page 8, lines 24-25) that the fractionation can be performed using one or more chromatographic techniques, which are defined (at page 9, lines 20-22) as "a technique that separates components of a mixture based on size, charge, molecular weight, hydrophilic/hydrophobic interactions, solvent interactions and/or specific binding interactions", and that such techniques include (at page 8, lines 26-29) column chromatography, HPLC, FPLC, matrix-affinity chromatography, reverse-phase chromatography, and electrophoretic separation.

In essence, the fractions and subfractions can therefore be obtained by any method known in the art and preferred by the one practicing the invention for fractionating and sub-fractionating biological samples. Applicants note that "a patent need not teach, and preferably omits, what is well known in the art." (*Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947, citing *Lindemann Maschinenfabrik v. American Hoist and Derrick*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984)). A requirement that the specification explain well-known fractionation techniques is therefore in error.

Which Sub-Fractions Would Possess The Claimed Functions

The Office Action appears to imply that one should be able to predict which of those fractions will have a desired activity before those fractions are made. Applicants strongly disagree with this interpretation of the claims. In the case of *In re Wands* (858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988)), it could not have been predicted *a priori* which hybridoma of those made would be active. The hybridomas needed to be screened. Indeed, absolute

predictability of the activity of embodiments which may be embraced within the claims is a not a requirement of the statute.

Furthermore, the claimed methods are methods of screening the helminthic parasite preparations for the ability to reduce an excessive Th1 immune response. The utility of the claims is the identification of those subfractions that contain the specified activity. A requirement of knowing ahead of time which fractions would possess the activity would therefore be in error.

How The Sub-Fractions Are Obtained And Used In The Assay

As discussed above, fractionation and subfractionation are defined in the specification. The fractions and subfractions can therefore be obtained by any method known in the art for fractionating and sub-fractionating biological samples.

The fractions and subfractions can then be assayed for activity (*i.e.*, reducing an excessive Th1 immune response) as provided in the specification. Such assays include histological analysis, analysis of cytokine and immunoglobulin profiles (see, *e.g.* page 21, lines 21-24), cell surface expression of Fcγ3 and MHC Class II molecules (see, *e.g.*, page 21, lines 24-28), analysis of mesenteric lymph node and spleens of affected animals for worm antigen or anti-CD3, serum for cytokines or immunoglobulins (see, *e.g.*, page 21, line 28-page 22, line 5). The specification also states that “IFN-γ, TNFα and IgG2a characterize a Th1 response, whereas IL-4, IL-5, IgE and IgG1 typify a Th2 reaction” (at page 22, lines 3-4).

In general, assays are described in the specification on page 21, line 21 to page 22, line 16. Specific assays are then discussed (*e.g.*, cytokine detection by flow cytometry at page 22, lines 17-29), ELISAs (page 23, line 1 to page 24, line 2), ELISPOT assays (page 24, lines 3-22), evaluation of disease (page 24, line 27 to page 30, line 8). *In vitro* and *in vivo* assays are also discussed at page 30, line 23 to page 34, line 20.

Infection of mice is shown in the examples, *e.g.*, Example 1 (page 36, line 12 to page 38, line 10). Down-modulation of an ongoing Th1 response is shown in Example 2 (page 38, line 11 to page 39, line 28, and Figs. 1-3), attenuation of Th1-type gut inflammation in mice by

treatment with helminths is shown in Example 3 (page 40, line 1 to page 43, line 26), down-modulation of Crohn's Disease in humans is shown in Example 6 (page 46, line 3 to page 48, line 2, and Fig. 4), down-modulation of ulcerative colitis in humans is shown in Example 7 (page 48, lines 3-17), and protection against multiple sclerosis in mice is shown in Example 8 (page 48, line 8 to page 52, line 18, and Figs. 5-10).

Applicants have therefore provided ample guidance on how the fractions and subfractions are obtained, and the assays in which they can be used.

The Specification Provides No Showing Of Fractionation Or A Sub-Fractionation Of Helminthic Preparations

The Office Action states that the specification provides no "showing" of fractionation or sub-fractionation of helminthic preparations. However, as discussed above, various methods of fractionating and sub-fractionating biological samples are known in the art, and "a patent need not teach, and preferably omits, what is well known in the art." (*Hybritech*, 231 U.S.P.Q. 81 (Fed. Cir. 1986)).

Furthermore, "[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be 'working' or 'prophetic.' " (Manual of Patent Examining Procedure (MPEP) § 2164.02). In fact, "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation." (MPEP § 2164.02, citing *In re Borkowski*, 422 F.2d 904, 908, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970)).

One of ordinary skill in the art would know of the existence of a variety of techniques of fractionating and sub-fractionating biological samples, and there is no requirement of an actual working example of every possible embodiment of the invention. The specification therefore provides sufficient guidance to enable one of ordinary skill in the art to practice the invention as claimed.

The Specification Is Silent On How One Would Perform The "Assay" Step In Vivo

Applicants respectfully disagree with the assertion that the specification is silent on how one would perform the assay step *in vivo*. As discussed above (under *How The Sub-Fractions Are Obtained And Used In The Assay*), *in vivo* assays are discussed at various points throughout the specification, *e.g.*, at page 30, line 23 to page 34, line 20, and in the Examples.

Sufficient guidance is therefore provided to enable one of ordinary skill in the art to practice the invention as claimed.

The Specification Provides No Guidance On What Parameters Or Markers Are Measured

The Office Action states that the specification provides no guidance on what parameters or markers are measured, how the parameters or marker are measured, or how samples are obtained.

Applicants respectfully disagree with this characterization of the specification. As stated above, a variety of parameters and marker can be measured, including cytokines, immunoglobulins, Fcγ3, MHC Class II molecules, anti-CD3, IFN-γ, TNFα, IgG2a, IL-4, IL-5, IgE and IgG1. Analysis of these parameters differentiate between a Th1 and a Th2 response.

Samples are discussed with assays, and also at page 8, lines 17-18 and page 16, line 19 to page 19, line 11, and also in the Examples.

Therefore, sufficient guidance is provided by the specification with regard to what parameters and markers are measured, how they are measured, and how the samples are obtained.

The specification therefore provides guidance sufficient to enable one of ordinary skill in the art to practice the methods as claimed. Applicants respectfully request that the rejection on enablement grounds be reconsidered and withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Office Action states that claim 26 is vague and indefinite by the use of the phrase “one or more further steps of fractionating and assaying”. The Office Action states that “it is unclear what steps would fall under the limitation of ‘a fractionating and assaying’ step”, and that “[i]t is equally unclear how one can have one step that both ‘fractionates’ and ‘assays’.”

Claim terms are to be interpreted in light of the intrinsic evidence (*i.e.*, the claims at issue, the specification, and the prosecution history. See, *e.g.*, *McGill Inc. v. John Zink Co.*, 736 F.2d 666, 673-675, 221 U.S.P.Q. 944, 948-951 (Fed. Cir. 1984), *cert. denied*, 105 S.Ct. 514 (1984); *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1569-1571, 219 U.S.P.Q. 1137, 1140-1141 (Fed. Cir. 1983)). Moreover, claims should be construed as they would be by those skilled in the art. *Fromson*, 720 F.2d at 1571, 219 U.S.P.Q. at 1142.

Applicants respectfully submit that one of ordinary skill in the art, upon reading the claims, would understand that the phrase “one or more further steps of fractionating and assaying” means that a fraction of step (d) of claim 24, that was found to reduce an excessive Th1 immune response, could itself be subjected to fractionation, thereby producing sub-fractions, each of which would be assayed for its ability to reduce an excessive Th1 immune response, thereby identifying sub-fraction(s) containing one or more components that reduce an excessive Th1 immune response.

Applicants therefore respectfully submit that claim 26 is clear on its face. However, in the interests of advancing prosecution, Applicants have amended claim 26 to recite that the fraction identified is further subjected to step (c) and then step (d), one or more times, so as to identify a sub-fraction containing one or more components that reduce an excessive Th1 immune response. The amendment is a re-phrasing of language already in claim 24, from which claim 26 depends. The amendment is therefore neither new matter, nor does it raise new grounds of search or consideration, nor has the scope of claim 26 been altered by the amendment.

Applicants respectfully request that the rejection of claim 26 be reconsidered and withdrawn.

The Office Action also states that claim 32 is vague and indefinite because “it is unclear how one would assay activity *in vivo*.” The Office Action states that the claim “fails to identify what, if any, assays would be considered an ‘*in vivo* assay’ to detect a reduction in an excessive TH1 immune response”.

As discussed above, numerous *in vivo* assays are provided in the specification, as well as several working examples. Applicants are not required to limit the claims to a single *in vivo* assay.

In vivo assays provided in the specification include evaluation of diseases such as inflammatory bowel disease, rheumatoid arthritis, lupus erythematosus, juvenile insulin-dependent diabetes mellitus (Type I), sarcoidosis, multiple sclerosis, autoimmune thyroiditis, colon polyps, colon cancer, allergic airway diseases, asthma and allergic rhinitis (see, *e.g.*, page 24, line 27 to page 30, line 8). *In vivo* assays are also discussed at page 30, line 23 to page 31, line 13. Animal models are provided at page 33, line 1 to page 34, line 20. Infection of mice is shown in Example 1 (page 36, line 12 to page 38, line 10), down-modulation of an ongoing Th1 response is shown in Example 2 (page 38, line 11 to page 39, line 28, and Figs. 1-3), attenuation of Th1-type gut inflammation in mice by treatment with helminths is shown in Example 3 (page 40, line 1 to page 43, line 26), down-modulation of Crohn’s Disease in humans is shown in Example 6 (page 46, line 3 to page 48, line 2, and Fig. 4), down-modulation of ulcerative colitis in humans is shown in Example 7 (page 48, lines 3-17), and protection against multiple sclerosis in mice is shown in Example 8 (page 48, line 8 to page 52, line 18, and Figs. 5-10).

Applicants respectfully submit that it is clear what is meant by an *in vivo* assay to assess the ability of a fraction or sub-fraction to reduce an excessive Th1 immune response, and request that the rejection on this basis be reconsidered and withdrawn.

The Office Action also states that claim 32 “fails to recite the active steps required in order to fulfill the stated objective of the method claim.”

There is no requirement that a method claim recite “active steps”, but simply that such a claim recite active verb usage beyond the phrase “the use of”. Applicant notes that it is MPEP

§ 2173.05(q) that discusses such indefinite “use” claims, providing examples such as “[a] process for using monoclonal antibodies of claim 4 to isolate and purify human fibroblast interferon” and “[t]he use of a high carbon austenitic iron alloy having a proportion of free carbon as a vehicle brake part subject to stress by sliding friction.” These claims are not analogous to Applicants’ claims which, by virtue of their depending from claim 24, recite such steps as “obtaining”, “producing”, separating” and “assaying”.

In stating that use claims must recite “active, positive steps”, MPEP § 2173.05(q) cites *Ex parte Erlich*, 3 U.S.P.Q.2d 1011 (Bd. Pat. App. & Inter. 1986). This case states clearly that “claims need not specifically outline any process steps” (at 1017, citing *Ex parte Bull*, 117 U.S.P.Q. 302 (Pat. & Trademark Off. Bd. App. 1957), but can “recite active, positive steps such as ‘bringing together . . .,’ ‘providing,’ and ‘maintaining.’ ”

Applicant’s claims fulfill this requirement for active, positive steps. Claim 24 recites a method comprising steps of “obtaining”, “producing”, separating” and “assaying”. Claim 32 depends from claim 24, and therefore incorporates all of the steps of that claim.

Claim 32 therefore recites active steps, and Applicants respectfully request that the rejection on this basis be reconsidered and withdrawn.

Rejections Under 35 U.S.C. § 103

The Office Action states that claims 24, 26 and 28-32 remain rejected under 35 U.S.C. § 103 as unpatentable over Pearce *et al.* (*J. Exp. Med.* 173:159-166, 1991), in view of Pearce *et al.* (*Proc. Natl. Acad. Sci. USA* 85:5678-5682, 1988).

The Office Action states that Pearce *et al.* (1991) discloses a method of identifying antigens from *Schistosoma mansoni* for the ability to reduce Th1 responses (abstract and pages 164-165), and that the method comprises preparing parasite antigens and screening them for the production of IFN γ or IL-5. The Office Action also notes that this reference does not explicitly disclose a method of preparing an helminthic parasite antigen comprising homogenizing, fractionating and identifying sub-fractions for activity.

The Office Action states that Pearce *et al.* (1988) discloses a method of preparing antigens from *S. mansoni*, comprising obtaining adult schistosomes, homogenizing them, centrifuging, and purifying by immunoaffinity chromatography, and that it therefore would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare schistosome antigens by homogenization and column chromatography, and then assaying the resulting fractions by the methods of Pearce *et al.* (1991) for the fractions' ability to reduce excessive Th1 responses. The Office Action states that schistosome antigens would be identified for their ability to reduce excessive Th1 responses because Pearce *et al.* (1991) specifically identify and compare antigens and their ability to down-regulate Th1 cytokine production.

The claims recite methods of screening helminthic preparations for "one or more components that reduce an excessive Th1 immune response." The phrase "a component that reduces an excessive Th1 immune response" is defined in the specification at page 9, lines 3-8 as a portion of a helminthic parasite preparation "that has activity in *in vitro* or *in vivo* assays for either a reduced Th1 response or an induced Th2 response." In addition, the term "excessive" Th1 immune response is defined in the specification at page 5, line 24 to page 6, line 2, as "a Th1 response in which the activity of T helper cells is elevated in an individual relative to the activity of such cells in an individual who is not affected by the disease. Typically, the elevation of the Th1 response in the diseased individual will be at least 2-fold, and possibly 5-fold - 10-fold above the Th1 response in an individual who is not diseased. Th1-type inflammations produce large amounts of IFN γ and TNF α , which in turn stimulate a strong cellular immune reaction."

Pearce *et al.* (1988) teaches vaccinating mice with paramyosin protein, and that "paramyosin was shown to stimulate T lymphocytes from vaccinated mice to produce lymphokines [e.g., γ interferon (IFN- γ)]" (Abstract, lines 13-16, emphasis added), and that "[I]ymphocytes from mice vaccinated with paramyosin were found to produce IFN- γ in response to living schistosomula" (Abstract, lines 23-28, emphasis added). As stated in Applicants' specification at page 5, line 28 to page 6, line 2, elevated IFN γ production is an excessive Th1 immune response. Pearce *et al.* (1988), therefore, does not teach a method of

reducing an excessive Th1 immune response, but rather, of causing an excessive Th1 immune response.

Pearce *et al.* (1991) teaches vaccination of mice with attenuated larval stages of the parasite in order to reduce subsequent infection by that parasite. The Abstract states that the data shows enhanced IFN γ synthesis by cells from vaccinated animals, and that "T cells from vaccinated mice of prepatently infected animals responded primarily with th1 lymphokines". Like Pearce *et al.* (1988), this reference does not teach a method of reducing an excessive Th1 immune response, but rather, of causing an excessive Th1 immune response.

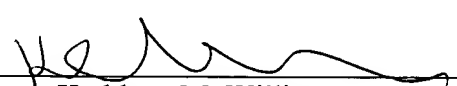
In contrast, Applicants' claims recite methods of screening for components that reduce an excessive Th1 immune response. Neither reference cited in the Office Action shows such a method, nor can they be combined in such a way so as to render obvious such a method. Rather, the references teach vaccination to reduce future infection, with both vaccination and the subsequent test infection causing an increase in synthesis of IFN γ and other products associated with an increase in the Th1 immune response. These references therefore represent a classic teaching away from Applicants' claims.

The references cited in the Office Action, either alone or in combination, therefore, fail to render obvious Applicants' claims, and Applicants respectfully request that the rejection on this basis be reconsidered and withdrawn.

Applicants submit that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of rejections over the claims of the present invention.

Respectfully submitted,

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Name: Kathleen M. Williams

Registration No.: 34,380

Customer No.: 29933

Palmer & Dodge LLP

111 Huntington Avenue

Boston, MA 02199-7613

Telephone: (617) 239-0100

Telecopier: (617) 227-4420

MARKED-UP VERSION OF AMENDMENTS:

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

Please amend claim 26 as follows:

26. (Twice Amended) The method of claim 24 wherein a fraction containing one or more components that reduce an excessive Th1 immune response is further subjected to steps (c) and (d) one or more times [further steps of fractionating and assaying], to identify a sub-fraction containing one or more components that reduce an excessive Th1 immune response.